SEHSC
SILICONES ENVIRONMENTAL, HEALTH AND SAFETY COUNCIL NORTH AMERICA

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April 20, 2006

CONTAINS NO CBI

TSCA Confidential Business Information Center (7407M)
EPA East – Room 6428
Attn: TSCA Section 8(e) Coordinator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: TSCA Section 8(e) Notification of Substantial Risk: *In Vitro* Mammalian Chromosome Aberration Test

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), as interpreted in the Statement of Interpretation and Enforcement Policy (68 Federal Register 33129; June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council of North America (SEHSC)[1], on behalf of its member companies, submits the following information. Neither SEHSC, nor any member company, has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings.

## Chemical Substance

1066-42-8 Dimethylsilanediol

8EHQ-05-15441

## Ongoing Study

*In Vitro* Mammalian Chromosome Aberration Test. BioReliance study number: AB21RP.331.BTL. (This study was conducted in compliance with the testing guidelines of the ICH (1996 and 1997) and the OECD (1998).)

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[1] SEHSC is a not-for-profit trade association whose mission is to promote the safe use of silicones through product stewardship and environmental, health and safety research. The Council is comprised of North American silicone chemical producers and importers.

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**Summary**

The test article, dimethylsilanediol (DMSD), was tested in an *in vitro* chromosome aberration assay using Chinese hamster ovary (CHO) cells, in both the absence and presence of an Aroclor-induced S9 activations system. A preliminary toxicity test was performed to establish the dose range for the chromosome aberrations assay. The chromosome aberration assay was used to evaluate the clastogenic potential of the test article. The dosing solution concentrations were adjusted to compensate for the purity (99.0%) of the test article.

Water was the solvent of choice based on the solubility of the test article and compatibility with the target cells. The test article was soluble in water at a concentration of approximately 50 mg/ml, the maximum concentration tested for solubility.

In the preliminary toxicity assay, the maximum dose tested was 5000 µg/ml. The test article was soluble in water and in the treatment medium at all dose levels tested at the beginning and conclusion of the treatment period.

Substantial toxicity (i.e., at least 50% cell growth inhibition, relative to the solvent control) was not observed at any dose level in all three exposure groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 625 to 5000 µg/ml for all three exposure groups (4- and 20-hour non-activated and 4-hour activated).

In the chromosome aberration assay, the cells were treated for 4 and 20 hours in the non-activated test system and for 4 hours in the S9-activated test system. All cells were harvested 20 hours after treatment initiation. The test article was soluble in water and in the treatment medium at all dose levels tested at the beginning and conclusion of the treatment period.

In the absence of both test article precipitation in the treatment medium and at least 50% toxicity, the highest dose level evaluated for chromosome aberrations was 5000 µg/ml in all harvests. Two additional lower dose levels were included in the evaluation. The percentage of cells with structural aberrations, in the non-activated 4-hour exposure groups was significantly increased (9.3% and 20.0%, respectively) above that of the solvent control at dose levels 2500 and 5000 µg/ml ($p \leq 0.01$ Fisher's exact test). The Cochran-Armitage test was also positive for a dose response ($p \leq 0.05$). The percentage of cells with numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control at any dose level ($p > 0.05$, Fisher's exact test).

The percentage of cells with structural aberrations in the S9-activated 4-hour exposure groups was significantly increased (11.5%, 21.0% and 13.0%, respectively) above that of the solvent control at dose levels 1250, 2500 and 5000 µg/ml ($p \leq 0.01$ Fisher's exact test). The Cochran-Armitage test was also positive for a dose response ($p \leq 0.05$). The percentage of cells with numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control at any dose level ($p > 0.05$, Fisher's exact test).

Initially, the non-activated and S9-activated 4-hours exposure groups were evaluated for chromosome aberrations and since a positive result was obtained in the non-activated 4-hour exposure group, the non-activated 20-hour continuous exposure group was not evaluated for chromosome aberrations.

**Summary Tables**

**Analysis of CHO cells treated with DMSD in the Absence of Exogenous Metabolic Activation**

| *Treatment µg/ml* | *Treatment Time* | *Mean Mitiotic Index* | *Cells Scored* | | *Aberrations per Cell (mean ± SD)* | *Cells with Aberrations* | |
|---|---|---|---|---|---|---|---|
| | | | Numerical | Structural | | Numerical,% | Structural,% |
| Water | 4 | 10.0 | 200 | 200 | 0.025 ± 0.157 | 3.5 | 2.5 |
| | | | | | | | |
| DMSD | | | | | | | |
| 1250 | 4 | 9.0 | 200 | 200 | 0.055 ± 0.250 | 3.5 | 5.0 |
| 2500 | 4 | 8.7 | 200 | 150 | 0.153 ± 0.857 | 7.0 | 9.3* |
| 5000 | 4 | 8.8 | 200 | 100 | 0.220 ± 0.462 | 0.0 | 20.0* |
| | | | | | | | |
| MMC[1] | | | | | | | |
| 0.2 | 4 | 6.5 | 200 | 100 | 0.620 ± 1.813 | 0.5 | 24.0* |

[1] Mitomycin C, CAS number 50-07-7
* $p \leq 0.01$, Fisher's Exact Test

**Analysis of CHO cells treated with DMSD in the Presence of Exogenous Metabolic Activation**

| *Treatment µg/ml* | *Treatment Time* | *Mean Mitiotic Index* | *Cells Scored* | | *Aberrations per Cell (mean ± SD)* | *Cells with Aberrations* | |
|---|---|---|---|---|---|---|---|
| | | | Numerical | Structural | | Numerical,% | Structural,% |
| Water | 4 | 10.6 | 200 | 200 | 0.015 ± 0.122 | 0.5 | 1.5 |
| | | | | | | | |
| DMSD | | | | | | | |
| 1250 | 4 | 8.2 | 200 | 200 | 0.195 ± 0.831 | 2.0 | 11.5* |
| 2500 | 4 | 7.9 | 200 | 100 | 0.410 ± 1.223 | 2.0 | 21.0* |
| 5000 | 4 | 8.5 | 200 | 200 | 0.215 ± 0.850 | 0.5 | 13.0* |
| | | | | | | | |
| CP[2] | | | | | | | |
| 10 | 4 | 5.9 | 200 | 50 | 3.240 ± 4.099 | 0.5 | 54.0* |

[2] Cyclophosphamide, CAS number 6055-19-2
* $p \leq 0.01$, Fisher's Exact Test

**Discussion**

DMSD is not a commercially available product. However, it was previously shown that hexamethyldisiloxane (HMDS), octamethylcyclotetrasiloxane ($D_4$), and decamethylcyclopentasiloxane ($D_5$) can be metabolized by animals to DMSD, and studies in humans with $D_4$ and $D_5$ have confirmed a similar metabolic pathway as seen in the animal studies. Under the conditions of the current *in vitro* chromosome aberration assay, DMSD was positive for the induction of structural, but negative for the induction of numerical, chromosome aberrations in CHO cells in both the non-activated and S9-activated test systems. A bacterial reverse mutation assay has also been conducted with DMSD and the results from this assay indicated that the test article is non-mutagenic.

**Actions**

Due to the seemingly equivocal results of the current study with DMSD, *in vivo* assay work will be conducted with DMSD to assess further the potential mutagenic effect, if any, of this substance.

SEHSC will notify U.S. EPA of any further relevant information that may be developed concerning this material. SEHSC also will provide U.S. EPA with the copy of the final report containing these study results when it is available. If you have any questions concerning this study, please contact me at (703) 788-6570, rmenning@sehsc.com, or at the address provided herein.

Sincerely,

Tracy Hill for Reo Menning

Reo Menning
Executive Director